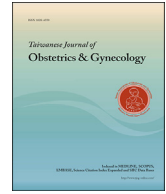




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Original Article

Posterior pelvic exenteration and retrograde total hysterectomy in patients with locally advanced ovarian cancer: Clinical and functional outcome



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ABSTRACT

Objective: To evaluate clinical outcomes and postoperative quality of life in patients affected by locally advanced ovarian cancer who underwent pelvic posterior exenteration with Hudson-Delle Piane radical retrograde hysterectomy.

Materials and Methods: Our study was done on a retrospective cohort using data from 22 patients who underwent surgery between 2010 and 2014 at the Gynecological Oncologic Center of Parma, Parma, Italy. **Results:** Residual disease after surgery (Sugarbaker index) was absent (CC-0) in 68% of cases. Tumor size was < 2.5 mm (CC-1) in 14% of cases and between 2.5 mm and 2.5 cm (CC-2) in 18% of cases. Complications during surgical procedure occurred in 64% of patients (14/22), but without severe consequences. Immediate postoperative complications (≤ 30 days) occurred in 82% of patients (18/22), and delayed complications (> 30 days) occurred in 23% (5/22) of patients. No patient died because of a complication. Urinary and rectal incontinence occurred in 5% and 16% of patients, respectively. Disease recurrence occurred in 58% of patients, median disease-free survival was 14 months (range, 6–36 months), and median overall survival was 21 months (range, 6–42 months).

Conclusion: Our study confirmed that pelvic posterior exenteration associated with retrograde radical hysterectomy represents the safest radical surgical approach to advanced ovarian cancer, which permits preservation of the pelvic autonomic nerve plexus and, therefore, bladder and colorectal functions.

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Introduction

Epithelial ovarian cancer (EOC) is the sixth most common malignancy among women in developed countries, with an estimated incidence of 100,300 new cases per year [1,2]. The standard treatment remains primary cytoreductive surgery [primary debulking surgery (PDS)], followed by different cycles of adjuvant platinum-based chemotherapy [3,4]. A primary approach based on interval debulking surgery (IDS) following neoadjuvant chemotherapy may be appropriate, especially in patients whose medical conditions do not permit primary surgery. Evidence concerning survival rates,

adverse events, and quality of life in patients subjected to this approach are still inconclusive [5,6].

Brunshwing et al [7], with a primary palliative intent, introduced the concept of pelvic exenteration (PE) in the treatment of advanced pelvic cancer. Occasionally, PE unexpectedly resulted in a long-term survival and permitted a definition of the surgical technique and the criteria for correctly selecting patients that would benefit from this extensive surgery [8].

PE is classified as anterior (APE), posterior (PPE), or total (TPE). APE consists of the removal of both reproductive tract and bladder, PPE consists of the removal of the reproductive tract along with recto-sigmoid colon, and TPE involves removing all anatomical structures listed above. Regarding the level of resection of pelvic viscera, we subclassify PE as supralevator (above the levator muscle), infralevator (preservation or resection of levator muscle), and with vulvectomy (extension or resection of the uro-genital diaphragm) [9,10].

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In consideration of the anatomical pelvic subversion, a retroperitoneal approach is designed for intact removal of a fixed ovarian-tumor en-bloc of the attached peritoneum, uterus, recto-sigmoid, and all surrounding structure [11–13]. Recent studies analyzing PPE efficacy and safety for the treatment of locally advanced EOC reported an overall survival ranging between 33 months and 49.4 months after surgery, confirming that PE represents a feasible surgical option offering an acceptable prognosis to highly selected patients with locally advanced-stage EOC [14–16].

Despite general agreement in describing the rates of intra-operative and early postoperative complication at ~30%, [8,9,17,18], little data are currently available concerning long-term complications, patient quality of life, and especially long-term effects of PPE on residual rectal and bladder functions. The aim of this study was to evaluate the onset of intra- and postoperative complications (both early and late complications), with particular attention to residual bladder and rectal functions 6-months post-surgery in patients with locally advanced EOC who underwent, by retroperitoneal approach, PDS or IDS with nerve-sparing PPE and retrograde radical hysterectomy according to the Hudson-Delle Piane (IRHDP) technique.

Materials and methods

We performed an observational, retrospective, cohort study on women who underwent PPE for locally advanced EOC over a period of 4 years between October 2010 and September 2014 at the Gynecology and Obstetrics Clinic, Department of Surgical Sciences, University of Parma, Parma, Italy. All patients agreed to the aim of the study and to the use of their data according to Italian Privacy Law (675/96).

We included patients < 82 years of age with an anesthetic risk ≤ 3 (ASA ≤ 3) and affected by primary EOC (independently from histotype) at stages II, III, or IV according to International Federation of Gynecology and Obstetrics (FIGO) classification [6] who underwent nerve-sparing PPE and IRHDP. All included patients presented with a pouch of Douglas or rectal involvement due to the direct extension of the neoplasm or serosal implantation. All patients underwent a laparoscopic staging, and a Fagotti score was applied. Those with a favorable score (< 8) underwent primary cytoreduction. When the score was > 8, IDS was performed after neoadjuvant chemotherapy [19,20].

In addition to PPE, standard-staging procedures (omentectomy, selective pelvic and lobo-aortic bulky node removal, peritoneal biopsies) and, in some cases, additional aggressive surgical procedures, including intestinal segment resections, peritonectomy, and splenectomy, were performed in order to achieve a complete cytoreduction.

For all patients, we collected data regarding age, parity, body mass index (BMI), pre-operative CA-125 serum value, stage and histotype of the disease, and timing of surgical operation (PDS or IDS). We also collected intra-operative data, including blood loss, operative time, need of blood transfusions, residual disease (RD) evaluated according to the Sugarbaker index [21], and intra-operative complications based on Clavien-Dindo classification [22]. The postoperative data collected included length of hospitalization, postoperative complications divided into early (< 30 days) and late (> 30 days) according to Clavien-Dindo classification, residual rectal and bladder functioning at 6-months post-surgery, residual rectal and bladder functions > 6-months post-surgery, recurrence rate, disease-free survival (DFS), overall survival (OS), and mortality index due to disease progression.

Evaluation of postoperative residual rectal and bladder function

To evaluate residual bladder function, all patients were asked to complete the validated short version of the Urogenital Distress

Inventory (UDI-6) questionnaire at 6-months post-surgery in order to detect any urinary disorders [23]. To evaluate residual rectal function, all patients were required to complete the validated Fecal Incontinence Severity Index (FISI) questionnaire at 6-months post-surgery, which allows detection of fecal incontinence disorder based on gas, mucus, solid, or liquid stools [24].

Surgical procedure

The first stage of the surgical procedure began with a longitudinal suprapubic incision and an exhaustive exploration of the abdominal cavity to evaluate the extent of the disease and possible contraindication for surgery (invasion of the mesenteric root, celiac region, hepatic pedicle, gastric serous membrane, the presence of peritoneal miliaria, or multiple inoperable tumor sites in the bowel). After abdomen and pelvic inspection, all patients underwent en-bloc PPE and IRHDP as follows. The retroperitoneal approach began with the bilateral ligation and section of uterine round and infundibulopelvic ligaments, the isolation of ureters to the bladder, the uterine artery, the iliac vessels, and the obliterated artery, with subsequent opening of pararectal spaces of Latzko and Okabayashi and of medial paravesical and Yabuki spaces [25,26].

After the identification of hypogastric nerves (which run ~2 cm below the ureters), the lateral pelvic peritoneum and bladder peritoneum were opened, creating a peritoneal flap that is cleaved from the bladder proceeding caudally toward the vesico-vaginal space. At the upper third of the vagina, the surgeon performed an anterior and then a posterior colpotomy, with the opening of recto-vaginal space to the rectal ampulla. The operation proceeded laterally, with the execution of a radical hysterectomy, type C1 (with nerve preservation), according to the classification of Querleu-Morrow (Figures 1 and 2) [27].

To perform the contemporary en-bloc resection of the rectum, the surgeon proceeded to the development of pararectal fossae and the retrorectal spaces with the isolation of Waldeyer's fascia, hypogastric nerves, and the superior pelvic plexus. The rectosigmoid was mobilized from its peritoneal attachments and divided 3–5 cm above the disease using a linear mechanic stapler (Endo GIA™, Covidien), followed by its being freed from its mesentery and divided below the disease process, allowing for en-bloc removal of the entire pelvic disease. Finally, an end-to-end anastomosis with a circular stapler (EEA™, Covidien) inserted into the anus was performed. Prophylactic ileostomy or colostomy was performed in cases of ultralow resection.

Results

Twenty two patients were eligible for the clinical study, with a mean age of 65 years (range, 47–82 years) and a mean BMI of 27 (range, 20.1–33.1). Pre-operative serum CA-125 levels were above normal in 81.8% of patients (mean, 1375.82 U/mL). Seventeen patients (77%) underwent PDS, followed by adjuvant chemotherapy. Only 23% of these (5 patients) underwent IDS following neoadjuvant chemotherapy [4–6 cycles of Carboplatin (area under the curve = 5) and 175 mg/mq Paclitaxel]. The average length of hospital stay was 16 days (range, 8–34 days), with a median of 13 days.

According to FIGO classification, stage IV patients accounted for 41% of all cases (9 patients), stage III-C accounted for 54% of all cases (12 patients), and only one patient presented with stage II-C disease at definitive diagnosis. Histological patterns for 95% of patients (21 cases) showed definitive diagnosis of high-grade serous carcinoma, with only one patient presenting with low-grade carcinoma. Detailed data are shown in Table 1.

Table 1
Patient characteristics.

Characteristics	
No. patients	22
Age (mean), y	65
BMI (mean)	27
Parity	
Nulliparity	36.4
Multiparity	63.6
Pre-operative Ca-125 serum:	
<1500 U/mL	81
>1500 U/mL	19
Histotype:	
High-grade serous carcinoma	95
Low-grade carcinoma	5
FIGO stage:	
FIGO stage IV	41
FIGO stage IIIC	54
FIGO stage IIC	5

Data are presented as %, unless otherwise indicated.

FIGO = International Federation of Gynecology and Obstetrics.

Rectosigmoid resection was performed in 18% of cases (4 patients), with left-hemicolectomy in 59% of cases (13 patients), total colectomy in 9% of cases (2 patients), and last ileal loop resection in 14% of cases (3 patients). After an end-to-end anastomosis, 18% of patients underwent prophylactic stoma, including ileostomy (1 patient) or colostomy (3 patients). Patients (68%; 15 cases) underwent pelvic lymphadenectomy. The mean number of lymph nodes removed was 16 (range, 2–42), and in eight patients (53%), they tested positive for metastatic involvement. Moreover, only 16 patients (73%) underwent selective lombo-aortic lymphadenectomy, with the mean number of lombo-aortic lymph nodes removed at 15 (range, 2–49), with positivity to metastatic spread detected in nine patients (56%). Six patients (27%) underwent splenectomy.

Sixteen patients (73%) required a partial resection of the diaphragmatic peritoneum due to metastatic spread (on the right side in 9 patients, the left side in 1 patient, and bilateral in 6 patients). Detailed data about concomitant surgical procedures necessary for complete cytoreduction are reported in Table 2.

The mean operative time was 520 min (range, 210–700 min), with a mean blood loss of 1100 mL (range, 800–2500 mL). The RD after surgery, according to the Sugarbaker index, was absent (CC-0) in 68% of cases, > 2.5 mm (CC-1) in 14% of cases, and between 2.5 mm and 2.5 cm (CC-2) in 18% of cases. We reported an intra-operative complication rate of 64% (14 patients). In 23% of cases (5 patients), an intra-operative hemorrhage (> 1500 cc) requiring packed blood-cell transfusion (a Grade-II complication based on Clavien-Dindo classification). Nine patients (41%) were affected by Grade-III complications requiring adjunctive-surgical procedures, and in particular, eight patients experienced an

iatrogenic diaphragmatic lesion during peritonectomy without opening the pleural cavity. In one patient, we reported an iatrogenic bladder lesion. All surgical lesions were promptly repaired and sutured.

Concerning early postoperative complications (≤ 30 days), we reported a total complication rate of 82% (18 patients), with 16 episodes classifiable as Grade-I or -II and eight episodes as Grade-III or -IV. Of the Grade-I and -II complications, we described three episodes of mild pleural effusion successfully treated by noninvasive mechanical ventilation and respiratory physiotherapy (Grade-I), nine episodes of worsening anemia (hemoglobin < 8 g/dL) that required packed blood-cell transfusion (Grade-II), two episodes of persistent hyperpyrexia (> 38°C) that required prolonged antibiotic therapy, one episode of bowel subocclusion requiring hospitalization, but not a second surgical procedure (Grade-II), and one episode of paresthesia of the left thigh successfully treated by corticosteroids (Grade-II). However, of the Grade-III and -IV complications, four patients underwent a second surgical laparotomy procedure due to one episode of peri-anastomotic fistula that required the performance of a colostomy, one episode of gastric perforation secondary to a pyloric ulcer successfully treated by suturing the gastric wall, and two episodes of anastomotic leakage that required performance of a total colectomy with a definitive ileostomy. Moreover, we reported one case of pulmonary thromboembolism that required transfer to the Intensive Care Unit.

Concerning late postoperative complications (> 30 days), we reported a total complication rate of 23% (5 patients). One patient presented with a *Clostridium difficile* infection (Grade-II) that was adequately treated with antibiotics, two patients showed an incisional hernia (Grade-IIIB), one patient had an episode of symptomatic lymphocele drained under sonographic guidance (Grade-IIIA), and one patient underwent a re-laparotomy for bowel occlusion due to postoperative adhesions that required an ileal resection (Grade-IIIB). We reported no cases of mortality due to postoperative complications. Detailed data regarding postoperative complications are reported in Table 3.

During the follow-up period (range, 6–47 months), we reported a median DFS of 14.3 months (range, 6–36 months) and a median OS of 21 months (range, 6–47 months). Eleven patients (58%) developed disease recurrence over a range of time between 6 months and 36 months, with a mean of 14.3 months. However we did not report cases of pelvic disease relapse. During the follow-up period, we detected subsequent extrapelvic metastases localization in four cases (peritoneal), three cases (aortic lymph nodal), three cases (hepatic), and one case of pulmonary involvement. The mortality index for the sample was 23% (5 patients) due to disease progression and recurrence.

Regarding residual bladder function at 6-months post-surgery, we reported only one case of moderate urinary distress symptoms according to UDI-6, with the patient reporting a total score of

Table 2
Surgical procedures in addition to IRHDP and rectosigmoid resection.

Type of surgical procedure	No. patients	Cases (%)
Left-hemicolectomy	13	56
Total colectomy	2	9
Last ileal loop resection	3	14
Ileostomy	1	0.22
Colostomy	3	14
Pelvic lymphadenectomy	15	68
Lombo-aortic lymphadenectomy	16	73
Omentectomy	22	100
Splenectomy	6	27%
Resection of the peritoneum of the diaphragmatic cupola	16	73

IDS = interval debulking surgery; IRHDP = IDS with nerve-sparing PPE and retrograde radical hysterectomy according to the Hudson-Delle Piane technique; PPE = posterior pelvic exenteration.

Table 3
Intra-operative and postoperative complications.

	No. patients	Cases (%)
Intra-operative complications		
Hemorrhage (>1500 cc)	5	23
Iatrogenic diaphragmatic lesion	8	53
Iatrogenic bladder lesion	1	0.22
Early postoperative complications (≤ 30 d)		
Pleural effusion	3	14
Anemia (Hb <8 g/dL)	9	
Hyperpyrexia (>38°C)	5	23
Bowel subocclusion	1	0.22
Left-thigh paresthesia	1	0.22
Peri-anastomotic fistula	1	0.22
Anastomotic leak	2	9
Gastric laceration	1	0.22
Pulmonary thromboembolism	1	0.22
Late postoperative complications (> 30 d)		
<i>Clostridium difficile</i> infection	1	0.22
Incisional hernia	2	9
Lymphocele	1	0.22
Bowel occlusion	1	0.22

Hb = hemoglobin.

10. All other patients did not show any symptoms of urinary incontinence 6-months post-treatment.

Regarding residual rectal function evaluated by FISI questionnaire > 6 months post-surgery, only one patient reported fecal incontinence twice weekly or more. One patient experienced moderate constipation, likely related to adjuvant chemotherapy treatment. We did not report any other cases of rectal function abnormalities. We excluded from rectal function evaluation patients who underwent total colectomy, a single case that required a definitive ileostomy, and all cases that required a second surgical procedure on the bowel due to postoperative complications (a total of 6 patients were excluded). During the early postoperative period, all patients had regular micturition, and any intermittent catheterization was required. Urinary and rectal incontinence occurred in 5% and 16% of patients, respectively.

Discussion

The pivotal point of EOC treatment is to obtain an optimal surgical cytoreduction, which is one of the most powerful predictors of DFS and OS in advanced stages of disease [28,29]. DFS and OS are significantly worse in patients with suboptimal debulking, and evidence does not demonstrate a survival benefit for a secondary cytoreductive procedure when an adequate attempt at primary debulking was undertaken [30]. Due to the anatomical continuity between rectum and uterus, it is not unusual in locally advanced EOCs to observe widespread involvement of rectosigmoid, adjacent peritoneum, anterior, or especially posterior pelvic compartments [15]. In light of this data, PE and, especially, PPE with a retroperitoneal approach that allows for total en-bloc resection of pelvic posterior compartment organs ideally should represent the most effective surgical procedure for achieving optimal debulking. Even given the heterogeneous results and those related to poor sample sizes and the retrospective design of almost all available literature on this topic, the efficacy of PPE has been confirmed by different studies describing median OS ranging between 27 months and 50 months and median DFS ranging between 18 months and 50 months in patients affected by stage III–IV EOC treated by PPE. [14–16,28,31–34]. In our study, we reported a DFS and OS that were slightly lower as compared to those reported in previously; however, this result may be explained by only four patients (18%) undergoing a 6-month follow-up.

Even if the efficacy of PPE in terms of OS and DFS is generally confirmed, the complication rate related to this surgical procedure is still very high. In our study, we reported an intra-operative complication rate of ~64% and a postoperative complication rate of ~82%. These data seem high as compared to previous studies; however, we emphasize that the majority of those studies analyzed only the most serious intra-operative and early postoperative complications, ignoring minor cases that affect overall patient quality of life [14,31,32]. Taking into account the most serious complications described (small-bowel obstruction, anastomotic leakage, enterocutaneous fistula, pelvic abscess, surgical site infection, sepsis, and thromboembolic events) [31,32], our data appear in agreement with available literature, describing a total of 11 patients affected by a Grade-III or –IV postoperative complications, of which the most serious involved three episodes of anastomotic fistulae, two episodes of anastomotic leakage, one episode of gastric perforation, one case of pulmonary thromboembolism, and one episode of bowel occlusion.

In our study, we included in the follow-up period the evaluation of residual bladder and rectal function at 6-months post-surgery. In our opinion, this is a very important for the evaluation of post-surgical patient quality of life. To our knowledge, bladder and rectal function after PPE for primary gynecological cancer, to the extent of pelvic autonomic nerve preservation, has not been well described, even in cases where lesions on the pelvic autonomic nerves are common complications associated with gynecologic surgery [35,36]. Where possible, all surgical interventions were performed with nerve-sparing techniques, saving the pelvic plexus upper and hypogastric nerves and allowing patients to maintain good bladder and rectal function. Through the administration of the validated UDI-6 and FISI questionnaires at 6-months post-surgery, we detected only two cases of moderate bladder and rectal dysfunction, respectively. These data are in agreement with the only available paper that evaluated residual bladder functioning after PPE using a nerve-sparing technique [37]. Given that the sample size of our study was too small to draw any final conclusions regarding the real value of this technique in preserving rectal and bladder function, future large-scale studies on this topic are required to validate these findings.

In conclusion, our data suggested that a nerve-sparing PPE and retrograde radical hysterectomy according to the IRHDP technique represents an effective surgical option in cases of locally advanced EOC. This procedure allows for minimization of metastatic peritoneal spread, ensuring an optimal cytoreduction and acceptable residual bladder and rectal function at 6-months post-surgery. The high rate of intra- and postoperative complications suggested that more efforts should be undertaken in pre-operative selection of patients who could benefit from this extensive surgery. A multidisciplinary approach between gynecologist, general surgeon, and oncologist remains pivotal to reducing complication rates and maximizing the efficacy and safety of this aggressive surgical option.

Conflicts of interests

The authors have no conflicts of interest relevant to this article.

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